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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,751	06/01/2001	Seo Young Jeong	0217-0006	4257

23117 7590 08/24/2006

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,751	JEONG ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006 and 14 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 29-45* is/are pending in the application.

4a) Of the above claim(s) *2,4,14-21,31-39,41,43 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-13,22-27,29,40 and 42* is/are rejected.

7)☒ Claim(s) *30 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is a reply to the Papers filed 16 March 2006 and 14 June 2006 in response to the Non-Final Office Action mailed 17 October 2005. Claims 2, 4, 14-21, 31-39, 41, 43 and 45 were withdrawn from consideration and claims 1, 3, 5-13, 22-30, 40, 42 and 44 were considered in the 17 October Office Action. Claim 28 was canceled and claims 1-4, 10-12, 18-20, 22-27 and 29-45 were amended in the 14 June Paper. Claims 1-27 and 29-45 are pending and claims 1, 3, 5-13, 22-27, 29, 30, 40, 42 and 44 are under consideration.

Response to Amendment and Arguments

Objection to and rejection of claim 28 is rendered moot by the cancellation thereof.

Drawings

Objection to Figure 19 as being unclear is withdrawn in view of the filing of a corrected drawing.

Specification

Objection to the disclosure because the legends for Figures 10, 11, 13 and 20 do not match the brief description and for failing to provide proper antecedent basis for the claimed subject matter is **withdrawn** in view of the amendments to the specification.

The disclosure **stands objected** to because of the following informalities: The brief description of Figure 8 refers to data for a DOTAP/DOPE squalene lipid emulsion. However, the only panel in Figure 8 appears to show data obtained for DOTAP/DOPE/diolein not DOTAP/DOPE squalene.

Appropriate correction is required.

Claim Objections

Objection to claim 42 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is **withdrawn** in view of the amendment thereof.

Claim Rejections - 35 USC § 112

Rejection of claims 1, 3, 5-13, 22-27, 29, 30, 40, 42 and 44 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter is withdrawn in view of the claim amendments.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in being directed to "the complex according to claim 3". There is no antecedent basis for a "complex" in claim 3, which is directed to a method of preparing an oil-in-water lipid emulsion. In the interest of compact prosecution, the claim has been examined

as being directed to the method of claim 3 wherein the aqueous phase further comprises 0.01-10% of a hydrophilic polymer or hydrophilic polymeric lipid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 7-13, 24, 26, 29, 30, 40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (1997) WO 97/11682.

Claims 1, 5, 7-13, 22, 26, 29 and 30 are directed to an oil-in-water lipid emulsion comprising 2-30% of non-triglyceride oil, 0.01-20% of one or more cationic lipid transfection agents, and water to 100%, or directed to a complex comprising said oil-in-water lipid emulsion and a biologically active material selected from DNA, RNA, antisense nucleic acid, polynucleotide and oligonucleotide.

Liu et al. teaches an oil-in-water lipid emulsion for delivering biologically active material comprising a total lipid component of from about 0.001 to about 20% with the remainder being aqueous carrier. (See especially p. 7, ¶ 2.) Liu et al. further teaches, of the total lipid, the amphiphile is preferably present in an amount from about 5 to about 80 weight % (p. 7, ¶3) and the oil component is present in an amount from about 10 to about 80 weight % of the total lipid components. Thus, in the composition of Liu et al., the amphiphile is present at approximately 0.0005% to approximately 16% of the total composition and the oil is present in an amount from about 0.0001 to about 16% of the total composition. Liu et al. further teaches that the oil component can be diethylglycerol (a non-triglyceride oil; see especially p. 10, l. 3) and that the amphiphile can be selected from any one of several cationic lipid transfection agents (e.g., N-[1-(1,2-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride; p. 10, ll. 15-16).

Thus, Liu et al. teaches an oil-in-water lipid emulsion comprising a non-triglyceride oil and a cationic lipid transfection agent, wherein the range of oil and cationic lipid concentrations contemplated by Liu et al. overlap with the ranges recited in the instant claims. "In the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP 2144.05. Therefore, the teachings of Liu et al. render obvious the oil-in-water lipid emulsion of the instant claims. Furthermore, as Liu et al. teaches that the oil-in-water lipid emulsion can be complexed with biologically active material including DNA, RNA and antisense RNA (see especially p. 18, ¶2), the teachings of Liu et al. also render obvious the complex of the instant claims. Therefore, the

instant claim 1 and the instant claim 22, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

In addition, the emulsion and complex of product claims 5, 7-13, 24, 26, 29 and 30 are found in the teachings of Liu et al. Liu et al. teaches that the composition can comprise polyethyleneglycol (p. 12, l. 12), which reads on the hydrophilic polymer of claims 5, 10 and 11. Liu et al. teaches that the composition can comprise phospholipids (e.g., phosphatidylelthanolamine, p. 12, l. 13 and p. 14, ll. 25-33) and nonionic surfactants (pp. 12-14), which reads on the phospholipid and nonionic surfactant of the instant claims 7 and 12. In the paragraph bridging pp. 10-11, Liu et al. teaches that the composition can comprise a variety cationic lipids including many of those recited in claim 8 and some of which comprise glycerol according to claim 9, which cationic lipids also read on the cationic polymer of claim 24. Liu et al. teaches that the composition can comprise various cholesterol compounds (e.g., p. 11, ll. 5-7) and/or DOPE (i.e., dioleoyl-sn-3-phosphatidylethanolamine; p. 14, l. 33), which reads on the emulsion comprising cholesterol or DOPE of claim 13. Liu et al. teaches the composition in normal saline or phosphate buffered saline (sentence bridging pp. 16-17), which comprise various salts according to the limitations of claim 26.

At p. 18, ll. 23-25 Liu et al. teaches that the composition can comprise "small molecular weight drugs such as cisplatin which enhance transfection activity". Given that Liu et al. teaches that cisplatin is included in order to enhance transfection activity, it would be obvious to one of ordinary skill in the art and one would be motivated to include both nucleic acid (i.e., to be transfected) and cisplatin in the same complex. Therefore, given that cisplatin is a known anticancer agent, the teachings of Liu et al. also render obvious the invention of claim 29.

On page 15, Liu et al. teaches a method of making the oil-in-water emulsion comprising combining the oil component and the cationic lipid transfection agent component and emulsifying oil and lipid mixture in an aqueous carrier, which method is the same as the method recited in the instant claim 42, and renders the claim as a whole obvious for the reasons stated herein above regarding obviousness of ranges.

Claim 3 recites a method of preparing an oil-in-water lipid emulsion, wherein the steps are ordered such that the cationic lipid is first mixed with the water and the oil is added to the aqueous-lipid mixture. Although Liu et al. does not teach a method comprising the steps in the order recited, the method as a whole would be obvious over Liu et al. because selection of any order of mixing ingredients is *prima facie* obvious in the absence of new or unexpected results. (See MPEP §2144.04 IV. *C.*) For this reason, the method of claims 3 and 40, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In view of the foregoing, the invention of claims 1, 3, 5, 7-13, 26, 29, 30, 40 and 42 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (*supra*), as applied to claim 1 herein above, in view of Hartounian et al. US Pub. No. 2002/0039596 (effective filing date 14 November 1997; previously made of record).

The limitations of claim 1 and the teachings of Liu et al. with regard thereto are discussed herein above. Liu et al. does not teach that the composition should comprise squalenes, although

Liu et al. does teach, "By oil component as used herein is meant any water immiscible component that is conventionally referred to as an oil." (P. 9, ll. 27-29.)

Hartounian et al. teaches methods of making liposome preparations (see throughout) and that squalenes are among the components that can be used in the production of liposomes. (See especially ¶0027.) Hartounian et al. does not teach liposome compositions comprising the oils, such as squalene, present at the proportion recited in the instant claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include squalene as the oil component in the composition of Liu et al. Motivation to combine the teachings of the prior art is found in the nature of the problem to be solved in the disclosure of Liu et al., which is to provide liposome compositions capable of delivering agents such as nucleic acids into cells, comes from the teaching of Liu et al. that any water immiscible component conventionally referred to as an oil might be used in the composition and from the teaching of Hartounian et al. that squalene is an oil having "vesicle forming capability" useful in the production of liposomal delivery vehicles (¶0027). Furthermore, the skilled artisan would recognize that squalene and the oils explicitly contemplated by Liu et al. are equivalents known in the liposome drug delivery art to be useful for the same purpose and, therefore, it would be *prima facie* obvious to substitute any one for the other[1].

[1] See, *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.). An express suggestion to substitute one equivalent component or process for another is not necessary t render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)

In view of the foregoing, the invention of claims 1 and 6 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 1, 22, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (*supra*), as applied to claims 1, 22 and 24 herein above, in view of Gao et al. (1996) *Biochem.* 35:1027-1036.

The limitations of claims 1, 22 and 24 and the teachings of Liu et al. with regard thereto are discussed herein above. Liu et al. does not teach that the composition should comprise the cationic polymer polylysine.

Gao et al. teaches that the inclusion of polylysine in various cationic liposome formulations potentiates transfection of many different cell types. (See especially the section entitled "*Potentiation of Cationic Liposome-Mediated Transfection in Vitro by Polycations*" commencing on page 1029, Table 1, Figure 1 and the caption thereto).

It would have been obvious to one of ordinary skill in the art to modify the cationic liposome composition taught by Liu et al. to include polylysine as taught by Gao et al. according to the composition of the instant claims. Motivation to combine these teachings comes from the nature of the problem solved by the composition of Liu et al., which is to provide a delivery vehicle for introducing nucleic acids and other molecules into host cells, and the advantage of potentiated delivery obtained by including polylysine in cationic liposome compositions which is demonstrated by Gao et al. In view of the art, considered as a whole, one of ordinary skill would

clearly perceive a benefit in modifying the composition of Liu et al. by the inclusion of polylysine.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the art in view of the fact that Gao et al. demonstrates enhancement of three distinct cationic liposome compositions by the inclusion of polylysine (see especially Fig. 1 and the caption thereto) and that enhancement was seen in a variety of cell types (see especially Table 1).

In view of the foregoing, the invention of claims 1, 22, 24 and 25 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 1, 22, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (*supra*), as applied to claims 1 and 22 herein above, in view of Benz et al. (1996) WO 96/14864.

The limitations of claims 1 and 22 and the teachings of Liu et al. with regard thereto are discussed herein above. Liu et al. does not teach that the composition comprising a targeting moiety.

Benz et al. teaches immunoliposomes that optimize internalization of a drug into target cells bearing a cell surface marker comprising a Fab' domain of an antibody that specifically binds to the characteristic marker. (See especially, the abstract, and the paragraph bridging pp. 4-5.) In the section entitled "C) Fab' Antibody Fragment" (see especially p. 20, ¶2), Benz et al. provides a variety of examples Fab' molecules targeted to various cell surface receptors that would be expressed on many of the cells listed in the Markush group of claim 27.

It would have been obvious to one of ordinary skill in the art to modify the cationic liposome composition taught by Liu et al. to include a targeting molecule as taught by Benz et al. according to the composition of the instant claims. Motivation to combine these teachings comes from the nature of the problem solved by the composition of Liu et al., which is to provide a delivery vehicle for introducing nucleic acids and other molecules into host cells, and the advantage of optimized internalization of the liposome vehicle into target cells bearing a characteristic cell surface marker as taught by Benz et al. (See especially the Abstract.) In view of the art, considered as a whole, one of ordinary skill would clearly perceive a benefit in modifying the composition of Liu et al. by the inclusion of a targeting moiety.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the art in view of the demonstrated efficacy of Fab' targeting demonstrated by Benz et al. (See especially Example 2.)

In view of the foregoing, the invention of claims 1, 22, 23 and 27 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Allowable Subject Matter

Claims 30 and 44 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Examiner
Art Unit 1636